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Two Dog-Related Infections Leading to Death: Overwhelming *Capnocytophaga canimorsus* Sepsis in a Patient With Cystic Echinococcosis

Raimonda Matulionytė[1], Ingrida Lisauskienė[2], Gintautas Kėkštas[2], Arvydas Ambrozaitis[1]
[1]Department of Infectious, Chest Diseases, Dermatovenerology and Allergology, Vilnius University,
[2]Centre of Anesthesiology, Intensive Therapy and Pain Treatment, Vilnius University Hospital Santariškių Klinikos, Lithuania

Key words: *Capnocytophaga canimorsus; Echinococcus granulosus; fulminant sepsis; dog-related infection.*

Summary. *Capnocytophaga canimorsus is a fastidious, capnophilic, fusiform, and filamentous gram-negative rod. It is part of the normal oral flora of dogs and cats and can cause an infection in humans, but is of generally low virulence in healthy individuals.*

A case of fatal sepsis due to Capnocytophaga canimorsus in a 46-year-old woman with clinically silent cystic echinococcosis discovered postmortem is present. She had been bitten by a dog 3 days before the symptoms appeared. The family had owned the dog for 4 years. A preliminary diagnosis of septic shock of unknown etiology with multisystem organ failure was established. Despite all the efforts, the patient died on the seventh day of hospitalization. Laboratory findings received postmortem showed Capnocytophaga canimorsus isolated from the blood culture after 7 incubation days. Autopsy showed a cyst in the liver with a fibrotic wall and necrotic eosinophilic interiors containing fragments of Echinococcus granulosus scolices.

In conclusion, an interaction possibly established long ago between the host and Echinococcus granulosus conditioned immunosuppression mechanisms developed by the parasite in this case, which can explain such an aggressive course of the infection with Capnocytophaga. Two dog-related infections were fatal in the middle-aged dog owner considered healthy before this hospitalization. Vigilance concerning recent exposure to dogs or cats and potential immunosuppression risk factors must be maintained in a patient presenting with clinical features of fulminant sepsis.

Introduction

Capnocytophaga canimorsus (*C. canimorsus*) is a fastidious, capnophilic, fusiform, and filamentous gram-negative rod. It is part of the normal oral flora of dogs and cats and can cause an infection in humans, but is of generally low virulence in healthy individuals (1). Presented here is a case of a fatal infection with *C. canimorsus* in a patient with cystic echinococcosis, another canine-related infection discovered postmortem. The interaction between the host and the parasite suggests cytokine-controlled polarization of the immune response and, therefore, parasite-induced immunosuppression, which can explain such an aggressive course of the infection with *Capnocytophaga*.

Case Report

A 46-year-old woman, a nurse, was admitted to the Intensive Care Unit of Vilnius University Hospital Santariškių Klinikos complaining of fever, weakness, abdominal pain, nausea, vomiting, and rapidly spreading petechial rash. The patient had a history of hepatitis B 7 years ago. She was a nonsmoker and nonalcohol consumer.

The illness started suddenly when the patient experienced fever with chills. Twelve hours later, she noticed redness in the face area and petechiae in her body. She was referred to the Emergency Department of Republican Vilnius University Hospital. On examination, the vital signs were stable. Other findings included petechiae on her face and limbs, and abdominal distention with diffuse tenderness. The hemoglobin level was 132 g/L with a white cell count of 4.5×10^9/L and a platelet count decreased to 15×10^9/L. Endoscopy revealed hemorrhagic esophagogastroduodenitis, and ultrasonography showed some fluid within the peritoneal cavity. The patient was transferred to Vilnius University Hospital Santariškių Klinikos for further assessment.

On examination in the emergency room of Vilnius University Hospital Santariškių Klinikos, she was obtunded and experienced tachypnea (respiratory rate, 30 per min) and hypotension (80/50 mm Hg). Her extremities were cold; she was mark-

Correspondence to R. Matulionytė, Department of Infectious, Chest Diseases, Dermatovenerology and Allergology, Vilnius University, Birutės 1, 08117 Vilnius, Lithuania
E-mail: raimonda@infek.elnet.lt

edly cyanotic with diffuse petechiae and generalized ecchymoses over the limbs and face. During examination, the patient suddenly became unconscious with the developed signs of shock. She was emergently transferred to the ICU where she was intubated and ventilated. Laboratory data showed severe metabolic acidosis (pH 6.87; pO_2, 25 mm Hg; pCO_2, 25 mm Hg; base excess, –29.6 mmol/L), hypoglycemia of 0.4 mmol/L, hyperlactemia of 18 mmol/L, coagulation disorders (activated partial thromboplastin time, >250 s; prothrombin activity, 17%; international normalized ratio, 2.87; and fibrinogen concentration, 0.22 g/L), hepatic failure (aspartate aminotransferase, 274 U/L; alanine aminotransferase, 125 U/L; alkaline phosphatase, 49 U/L; serum bilirubin, 53 μmol/L; direct bilirubin, 36 μmol/L), renal failure (blood urea nitrogen, 9.3 mmol/L; creatinine, 240 μmol/L), increased inflammatory markers (C-reactive protein, 125 mg/L; procalcitonin, >10 ng/mL), and some electrolyte disorders (hypernatremia, 171 mmol/L; hypocalcemia, 1.78 mmol/L). A radiograph of the chest and echocardiography were unremarkable. A Foley catheter was placed, but no urine was obtained. A rigidity of the neck and positive Kernig's and Brudzinski's signs on the left were found during a neurologist's consultation. A lumbar puncture was performed after platelet transfusion. Cerebrospinal fluid analysis showed a leukocyte count of 11 leukocytes per mL, with 100% of lymphocytes, glucose level of 4.91 mmol/L, and protein level of 5.16 g/L. A computed tomography (CT) scan of the head was unremarkable. A CT scan of the chest and abdomen showed mediastinum adenopathy and a cyst in the porta hepatic of 4.3×4.3×4.6 cm in size with heterogeneous interiors and a calcified wall.

A preliminary diagnosis of septic shock of unknown etiology with multisystem organ failure including disseminated intravascular coagulation was established. Empiric antibiotic therapy with imipenem was initiated after two blood cultures had been obtained. Resuscitative and supportive measures included mechanical ventilation; massive colloid and crystalloid fluid infusions; vasopressor therapy with norepinephrine; and fresh-frozen plasma, platelet, and packed red blood cell transfusions. Progressive cyanosis with increased mottling and hemorrhagic necrosis developed in her limbs and face.

As the source of infection was still unclear, the patient's family was re-questioned about the conditions of the illness. The interview revealed that 3 days before the symptoms, her dog had bitten her right index finger. The family had owned a dog for 4 years. On examination, a 3-cm scratch without the signs of infection was found.

The patient's condition worsened on the next day. Progression of renal failure required continuous veno-venous filtration. She was bleeding from her nose and stomach. A laboratory report showed intracytoplasmic and extracellular fusiform rods from the peripheral blood smear.

On the third day of hospitalization, worsening inferior abdominal pain led to exploratory laparotomy, which showed 200 mL of serosanguineous fluid in the abdominal cavity, focal liver necrosis, and degenerating cysts in the ovaries. Antibacterial therapy was supplemented with vancomycin.

On the fifth day of hospitalization, the patient's condition complicated with right spontaneous pneumothorax. A chest tube was introduced for continuous air drainage. Despite all the efforts, the patient died on the seventh day of hospitalization.

A laboratory report, which was received postmortem, showed *C. canimorsus* from the blood culture after 7 incubation days. Cerebrospinal fluid, abdominal cavity fluid, and vaginal secretion cultures were negative.

Autopsy revealed necrosis focused in the liver, kidneys, and adrenal glands, gangrenous ecthyma in the skin, and a cyst in the liver with a fibrotic wall and necrotic eosinophilic interiors containing fragments of *Echinococcus granulosus* scolices.

Discussion

C. canimorsus was first isolated in 1976 from blood and spinal fluid of a patient after a dog bite. Since then, the cases of infection with *Capnocytophaga* spp. have been published with an increasing frequency. It is probably associated with several underlying factors, including an increasing number of pet owners, greater opportunities for animal bites, enhanced laboratory techniques to recover this bacterium from clinical material (2), and better awareness about the infection. However, *Capnocytophaga* spp. infection rates are still low. In Denmark, the incidence of this condition is estimated to be 0.5 case per 1 million people per year (3). The presented patient has been a sole documented case in Vilnius University Hospital Santariškių Klinikos.

C. canimorsus spreads to humans by bites, scratches, or less invasive forms of animal-human contact as simple licking by a dog or occasionally by a cat. As the name implies, up to 56% of patients had a history of a dog bite (1, 2, 4).

C. canimorsus is phagocytized and replicates intracellularly in the macrophages and has characteristics of a toxic phenotype (5). Commensal bacteria often do not trigger an inflammatory response, but instead, in some cases, have the capacity to actively turn it down, preventing the progression from an acute to chronic state. Recent observation has shown that *C. canimorsus* possesses both passive and active mechanisms of immune evasion (6).

Most infections with *Capnocytophaga* occur in persons with an impaired immune function or with

a significant underlying disease, although a few cases of a life-threatening infection in previously healthy people have been documented. The infection is most often documented in middle-aged or older people (1, 3). Asplenia or functional hyposplenism and alcohol abuse are the known risk factors for a disseminated infection with *C. canimorsus* (1–3). The use of glucocorticoids or chemotherapy is seldom associated with *C. canimorsus* infections (1). There have been so far no cases of infection with *C. canimorsus* in patients with the acquired immunodeficiency syndrome. In our case, the postmortem confirmation of cystic echinococcosis was a key point explaining such an aggressive course of infection with *Capnocytophaga* in a previously healthy woman. As it is natural in cystic echinococcosis, the illness had been clinically silent before this hospitalization. The disease was suspected after an incidentally discovered cyst during abdominal scanning during the hospitalization, and autopsy findings confirmed this suspicion.

The interplay between the host and the parasite suggests immunosuppression mechanisms used by the parasite for evasion and prolonged infestation in the host reducing his/her immune response to the parasite specifically and to foreign antigens in general. This interaction may be explained in terms of the effects of cytokines controlling polarization to the Th1 (INF-γ, IL-2, and IL-15) or Th2 (IL-4, IL-5, IL-6, IL-10, and IL-13) arms of the immune response. In echinococcosis, early Th1-polarized cytokine production, which can kill the metacestodes at the initial stages of development, shifts to a predominant Th2-type profile in the later chronic stage (7, 8). Th2 cytokines are responsible for the inhibition of parasite killing especially because of the "anti-inflammatory" potency of IL-10 (7, 9). In excess, the Th2 response naturally counteracts the Th1 cytokine-mediated microbicidal action and facilitates the persistence of infection (10–12). This phenomenon becomes particularly evident in concomitant infections caused by intracellular pathogens. In the case described above, this interaction favorable to the survival of echinococcus manifested by uncontrolled sepsis due to *C. canimorsus*.

The infection occurs generally 2 to 3 days after an animal bite or a scratch, but symptoms can appear later, after up to 2 to 4 weeks. *C. canimorsus* has been associated with a variety of conditions, including self-limiting disease with transient hyperthermy, cellulitis, meningitis, endocarditis, mycotic aortic aneurysms, and overwhelming sepsis. These fulminant septicemias are commonly complicated by disseminated intravenous coagulopathy (DIC), multiorgan failure, and septic shock (1, 13). As in our case, common initial symptoms are diarrhea, abdominal pain, and vomiting (2, 3). Severe abdominal pain led to exploratory laparotomy. Patients with DIC present with cyanotic mottling of the skin, peripheral cyanosis, petechial or ecchymotic purpura, which may evolve into peripheral gangrene. The clinical features of septicemia due to *C. canimorsus* are not specific. The fulminant course can mimic meningococcal septicemia. To suspect the diagnosis of septicemia due to *C. canimorsus*, it is important to know if the patient has recently had a close contact with a dog or a cat.

Contrary to low virulence of *C. canimorsus*, the mortality rate is high once systemic infection has developed. The case-fatality rate from reports describing large series is about 30%. Septic shock and DIC carry a poor prognosis (1–3).

Capnocytophaga is difficult to grow by standard culture methods, and a reference laboratory is needed for identification. Only one-third of the 56 isolates forwarded to California's Microbial Diseases Laboratory in a 32-year period were submitted with the correct species identification (2). The bacterium grows slowly, and more than 5 days are often required before identification is possible. The major phenotypic characteristics of *C. canimorsus* include the positive results of tests for oxidase, catalase, arginine dihydrolase, and *o*-nitrophenyl-β-D-galactopyranoside and negative reactions for urease, nitrates, and indole. The growth might be enhanced by the addition of rabbit serum and incubation in a carbon dioxide-enriched environment (2). Many laboratories are unable to presumptively identify *C. canimorsus* isolates, commonly reporting these strains as either gram-negative rods or fastidious gram-negative bacilli. The reasons for this may be the lack of familiarity with the organism, the lack of appropriate biochemical tests, or the use of commercial identification systems not designed for identifying fastidious microorganisms (2). Molecular techniques have recently improved the detection and identification of *Capnocytophaga* (2).

Gram staining of peripheral blood or buffy-coat smear is valuable and may provide an earlier diagnosis, permitting to evidence gram-negative bacilli within neutrophils (13). In our case, as in many reported cases, the whole blood smear was positive for gram-negative intracellular rods possibly suggesting high-level bacteremia. In a proper clinical setting, it allowed a presumptive diagnosis of infection with *C. canimorsus*.

The fastidiousness of *Capnocytophaga* makes antibiotic susceptibility testing difficult in practice, and antimicrobial treatment for septicemia due to *C. canimorsus* is often initially empiric (14, 15). In vitro studies have evidenced a wide susceptibility of this bacterium to antibiotics. Although β-lactamase production is increasing in other *Capnocytophaga* spp., it has not been reported in *C. canimorsus* (1,

14, 15). Penicillin is considered the treatment of choice. *Capnocytophaga* spp. are typically susceptible to clindamycin, linezolid, tetracycline, chloramphenicol, imipenem, and β-lactamase inhibitor combinations. Susceptibility to other antimicrobial agents varies (14). Polymicrobial infections after an animal bite and possible presence of β-lactamase-producing strains warrant broader first-line coverage with antibiotics (1, 14). In high-risk patients with predisposing factors (immunodeficiency, splenectomy, and alcoholism) and infection complications, imipenem/cilastatin should be preferred, considering that *Capnocytophaga* strains are always susceptible to this combination (14, 15).

Based on the Cochrane review, there is no evidence that the use of antibiotics after cat or dog bites is effective in preventing a bite wound infection (16).

Conclusions

An interaction possibly established long ago between the host and *Echinococcus granulosus* conditioned immunosuppression mechanisms developed by the parasite in this case. Two dog-related infections were fatal in the middle-aged dog owner considered healthy before this hospitalization. Vigilance concerning recent exposure to dogs or cats and potential immunosuppression risk factors must be maintained in a patient presenting with clinical features of fulminant sepsis.

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Statement of Conflict of Interest

The authors state no conflict of interest.

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